OIPE JC133
SEP 27 2004
PATENT & TRADEMARK OFFICE

Docket No.: 020547001910
(PATENT)
Client Ref. No. 010012.05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Robert L. ARSLANIAN et al.

Application No.: 09/957,483 Art Unit: 1652

Filed: September 19, 2001 Examiner: K. Kerr

For: PRODUCTION OF POLYKETIDES DECLARATION UNDER 37 C.F.R. §1.132 OF DR. ROBERT ARSLANIAN

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

I, Robert L. Arslanian, state as follows:

1. I am a co-inventor of the above-referenced patent application.

2. My education includes a Bachelor of Science in Chemistry from Colorado State University, Fort Collins, Colorado, and a Ph.D. in Organic Chemistry, also from Colorado State University. I have been employed since 1999 by Kosan Biosciences, Inc., and presently hold the title of Principal Research Investigator. I have previously been employed by Shaman Pharmaceuticals, Inc., Hauser, Inc., and Vipont Pharmaceuticals, Inc. I have over 14 years industrial experience in the purification of small molecules from fermentation and terrestrial plant sources. My *curriculum vitae* is attached as Exhibit A.

3. As I understand it, PCT publication WO 99/42602 by Hoffman et al. ("Hoffman"), pages 10 and 38, has been cited in an Office Action as describing crystallization of epothilone.

4. The Hoffman reference described crystallization of epothilone A and B but did not describe crystallization of epothilone D.

5. Hoffman described crystallization of epothilone A and B using single- and double-solvent systems in which both solvents were organic but did not describe crystallization of epothilone D, or any epothilone, from a binary solvent system in which water is the forcing solvent.

6. I, or a scientist working under my direction, attempted to obtain epothilone D crystals using the methods generally described in Hoffman for crystallization of epothilone A and B. Specifically, we tried to crystallize epothilone D from isopropyl alcohol, methanol and ethyl acetate without success (0.5 grams 93% pure epothilone D was dissolved in 5 ml isopropyl alcohol, methanol or ethyl acetate, transferred to a 20 ml scintillation vial, capped, stored at -20°C for 4 hours, and inspected for formation of crystals). We also tried using a binary solvent system containing a non-polar forcing solvent without success (0.5 grams 93% pure epothilone D was dissolved in 5 ml ethyl acetate, transferred to a 20 ml scintillation vial, and 1 ml toluene was added dropwise; the vial was capped, stored at -20°C for 4 hours, and inspected for formation of crystals).

7. As described in the specification of the above-referenced patent application, we were able to obtain epothilone D crystals using a binary system in which water was used as the forcing solvent. Without intending to be bound by a specific mechanism, I hypothesize that our method was successful because the crystalline epothilone D produced is a hemihydrate. In contrast, so far as I am aware, the epothilone A and epothilone B crystals described in the scientific literature at the priority date of the present application, and still today, are anhydrous. Hoffman did not suggest that crystalization using water as a forcing solvent would promote

crystal formation of any epothilone. The advantage of using water as a forcing solvent for epothilone D crystallization was unexpected.

8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 09/24/04

Robert L Arslanian

Robert L. Arslanian, Ph.D.

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EXHIBIT A

CURRICULA VITAE

Kosan Biosciences, Inc
Phone 510-731-5278
arslanian@kosan.com

Robert Arslanian

Qualifications

Over 14 years industrial experience in the purification of small molecules from fermentation and terrestrial plant sources. Developed scalable purification processes in support of large-scale production efforts. Experienced in scale-up and process optimization.

Education

1986 – 1990 Colorado State University, Fort Collins, CO
Ph.D. Organic Chemistry

1982 – 1986 Colorado State University, Fort Collins, CO
B.S. Chemistry

Professional Experience

Kosan Biosciences, Inc. Hayward, CA

July 04 – present

Principal Research Investigator I
On-site consultant for overseas contract manufacturing projects. Experienced in writing and reviewing SOP's. Developed HPLC methods used in tracking and assaying intermediate and final product process streams.

May 01 – July 04

Senior Scientist II
Developed scalable, high yielding purification process, which produced crystalline cGMP material for use as anticancer drug in Phase 1 clinical trials. Primary inventor on patent application for anti-cancer drug.

March 99 – May 01

Senior Scientist I
Purification of polyketides from 5-1000 L fermentation cultures. Experienced in the isolation of selected target molecules from cultures containing as little as 1 mg/L. Isolated 0.01-50 g of selected polyketides as purified compounds.

1997 - 1999	Shaman Pharmaceuticals, Inc. **Senior Scientist I** Managed resources in purification scale-up for diabetes project. Isolation and purification of small molecules from terrestrial plant sources. Produced 1-10 g of purified compounds for use in diabetic rat model. Inventor on patent application for a stabilized anti-diabetes drug.	S. San Francisco, CA
1991 - 1997	Hauser, Inc. **Senior Chemist** Purification of plant secondary metabolites for use in pharmaceuticals and nutritional supplements. Developed second-generation chromatography step for use in GMP taxol production. Reduced production costs by changing to a reusable sorbent that supported high loading chromatography conditions. Developed purification process for the production of a natural beta-carotene product. Developed process that produced kilogram quantities of purified michellamine B, a potential anti-AIDS drug that was being investigated by National Cancer Institute.	Boulder, CO
1990 - 1991	Vipont Pharmaceutical, Inc. **Senior Chemist** Investigated new methods for the isolation and purification of benzophenanthridines used in company's oral care products. Interacted with contract drug manufacturer. Carried out stability testing on formulated products.	Fort Collins, CO
Professional Memberships	American Chemical Society	
Publications	Arslanian, Robert L.; Tang, Li; Blough, Shannon; Ma, Wei; Qiu, Rong-Guo; Katz, Leonard; Carney, John R. "A New Cytotoxic Epothilone from Modified Polyketide Synthases Heterologously Expressed in *Myxococcus xanthus*." Journal of Natural Products (2002), 65(7), 1061-1064. Woo, Elaine J.; Starks, Courtney M.; Carney, John R.; Arslanian, Robert; Cadapan, Lawrence; Zavala, Stefan; Licari, Peter. "Migrastatin and a New Compound, Isomigrastatin, from *Streptomyces platensis*." Journal of Antibiotics (2002), 55(2), 141-146.	

EXHIBIT A

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Cadapan, L. D.; Arslanian, R. L.; Carney, J. R.; Zavala, S. M.; Small, P. L.; Licari, P. "Suspension Cultivation of *Mycobacterium ulcerans* for the Production of Mycolactones." FEMS Microbiology Letters (2001), 205(2), 385-389.

Arslanian, Robert L.; Bailey, David T.; Kent, Michael C.; Richheimer, Steven L.; Thornburg, Kelly R.; Timmons, Daniel W.; Zheng, Qun Y. "Brevitaxin, a New Diterpenolignan from the Bark of *Taxus brevifolia*." Journal of Natural Products (1995), 58(4), 583-5.

Stermitz, Frank R.; Arslanian, Robert L.; Castro, Oscar. "Flavonoids from the Leaf Surface of *Godmania aesculifolia* (Bignoniaceae)." Biochemical Systematics and Ecology (1992), 20(5), 481.

Arslanian, Robert L.; Anderson, Tara; Stermitz, Frank R. "Chemistry of the Scrophulariaceae. Part 16. Iridoid glucosides of *Penstemon ambiguus*." Journal of Natural Products (1990), 53(6), 1485-9.

Arslanian, Robert L.; Mondragon, Benny; Stermitz, Frank R.; Marr, Kendrick L. "Constituents of *Zanthoxylum* 13. Acyl Histamines and a Rare Protopine-Type Alkaloid from Leaves of *Zanthoxylum dipetalum*." Biochemical Systematics and Ecology (1990), 18(5), 345-7.

Arslanian, Robert L.; Harris, Guy H.; Stermitz, Frank R. "New Quinolizidine Alkaloids from *Lupinus argenteus* and Its Hosted Root Parasite *Castilleja sulphurea*. Stereochemistry and Conformation of Some Naturally Occurring Cyclic Carbinolamides." Journal of Organic Chemistry (1990), 55(4), 1204-10.

Arslanian, Robert L.; Stermitz, Frank R.; Castedo, Luis. "3-Methoxy-5-hydroxyflavonols from *Tillandsia purpurea*." Journal of Natural Products (1986), 49(6), 1177-8.

Arslanian, Robert L.; Harris, Guy H.; Stermitz, Frank R. "Chemistry of the Scrophulariaceae. 7. Some Iridoid Glucosides, Including the New 6-deoxycatalpol, from Indian Paintbrush Species Related to *Castilleja miniata*." Journal of Natural Products (1985), 48(6), 957-61.

Patents

Arslanian, Robert L.; Carney, John; Metcalf, Brian. Epothilone Compounds and Methods for Making and Using the Same. U.S. Patent 6,589,968, July 8, 2003.

Licari, Peter; Arslanian, Robert; Cadapan, Lawrence; Carney, John. Fermentation and Purification of Mycolactones. U.S. Patent 6,562,602, May 13, 2003.

Bailey, David T.; Daughenbaugh, Randall J.; Arslanian, Robert; Kaufmann, Leonard A.; Richheimer, Steven L.; Liu, Zhengjie Z.; Piffarerio, James M.; Kurtz, Chris J. Mixed Carotenoids and High Purity Beta-Carotene by Solvent Extraction of *Dunaliella salina*. U.S. Patent Application 2002082459, June 27, 2002.

Fort, Diana M.; Arslanian, Robert L.; Inman, Wayne D. Pharmaceutical Compositions Containing Stabilized Bicyclo [3.3.1] nonenes. WO Patent Application 2000054785, September 21, 2000.